



<b>Office Action Summary</b>	Application No.	Applicant(s)	
	09/472,558	BAHRAMIAN ET AL.	
	Examiner	Art Unit	
	Peter Paras	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☐ Responsive to communication(s) filed on 04 January 2001.
- 2a) ☐ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☐ Claim(s) 1-56 is/are pending in the application.
- 4a) Of the above claim(s) 28-49, 51 and 53-56 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) 1-27, 50 and 52 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on 27 December 1999 is: a) ☐ approved b) ☒ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

#### Attachment(s)

- |   |  |
|---|--|
| 15) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 18) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s) _____   |
| 16) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 19) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 17) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>g</u> | 20) <input type="checkbox"/> Other   |

Applicants' amendment filed on January 4, 2001 (Paper No. 9) has been entered. Claims 1-3, 11-12, 16-17, 22, 24-27, 50 and 52 have been amended. Claim 1-56 are pending. Claims 1-27, 50 and 52 are currently under consideration. Claims 28-49, 51, and 53-56 have been withdrawn from consideration as they are directed to a non-elected invention.

Prior rejections not made of record in the instant Office action have been withdrawn in view of Applicants' amendments to the claims.

***Claim Rejections - 35 USC § 112, 1<sup>st</sup> paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-27, 50 and 52 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a knockout mouse, comprising embryonic stem (ES) cells which have been genetically modified, such that expression of an endogenous gene has been reduced, using a muting transgene, does not reasonably provide enablement for a method of producing a knockout animal of any and all species comprising ES cells which have been genetically modified by a muting transgene or a pharmaceutical composition comprising a nucleic acid composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The rejection of claims 11-27, 50,

and 52 is maintained for the reasons of record advanced in Paper No. 5, on pages 4-11 of the Office action.

Applicant's arguments have been fully considered but they are not persuasive. Applicants assert that it was not intended to enable knock-out transgenic animals or gene therapy as the claims of the instant application are directed to compositions and methods for muting gene expression in animal cells. Applicants argue that the term "muting" is distinct from knockout techniques rather meaning "a method of using transient non-integrated transgene to reduce expression of an endogenous gene. See page 6 of the amendment. Applicants believe that muting of expression is an alternative to engineering a knock-out animal. Applicants allege that the specification provides many working examples that demonstrate muting of expression of an endogenous gene and that substantial muting "without integration or stable expression" can be achieved, and is thereby not unpredictable to expect. See page 7 of the amendment. Applicants also assert that the present invention does not claim that the muting method be used to treat any disease and that the claims do not pertain specifically to a therapy method (although the claims do not exclude the possibility that the claimed methods can be used in therapy in the future). See page 8 of the amendment.

In response, the Examiner acknowledges the summary of the invention provided by Applicants. Applicants have attempted to distinguish the claimed method of muting an endogenous gene from methods of creating knockout animals or methods of gene therapy. The Examiner however is of the opinion that the claims as written do not differ

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in interpretation from a method of producing a knockout animal or a method of gene therapy. Although Applicants allege that the claims are not directed to methods of producing a knockout animal or methods of gene therapy the specification provides support for such interpretations. The claims, however remain directed to *in vivo* methods of muting expression of an endogenous gene. It is unclear how muting can occur *in vivo* as the muting nucleic acid is not integrated into the host genome. Furthermore, the specification does not provide any working examples that demonstrate muting *in vivo* as claimed. Applicants also allege that "muting" means reduced expression of an endogenous gene. The Examiner disagrees as muting can mean reduction or elimination; the specification provides support for elimination of expression on page 13, last paragraph. Accordingly, for the reasons of record and as discussed in the preceding paragraph the rejection of claims 11-27, 50, and 52 under 35 U.S.C. 112, first paragraph is maintained.

***Claim Rejections - 35 USC § 112, 2<sup>nd</sup> paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-27 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection of claims 1-27 under 35 U.S.C. 112, second paragraph is maintained for the reasons advanced in Paper No. 5, on pages 3-4 of the Office action. Claims 50 and 52 as amended are encompassed in the standing

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rejection under 35 U.S.C. 112, second paragraph by dependency on claims 11 and 25 respectively.

Applicant's arguments have been fully considered but they are not persuasive. Applicants argue that the description clearly defines muting as a reduction in expression, rather than abolition of gene function. See page 8 of the amendment.

In response, the Examiner firmly asserts that the claims do not define the meaning of "muting". The Examiner maintains that "muting" can mean either completely abolished or only reduced.

Applicants argue that the term "substantially homologous" is clear to one ordinarily skilled in the art. Applicants further argue that "substantially homologous" is often used in US patent practice to describe similarity between two non-identical but closely related nucleic acid sequences.

In response, the Examiner asserts that the term "substantially homologous" is indefinite as it is a relative term not defined by the claims or specification. It is unclear how homologous the muting transgene must be to the endogenous gene.

Amendments to the claims have necessitated the following new ground of rejection:

Claims 26-27 and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "substantially transient" in claim 26 is a relative term which renders the claim indefinite. The term "substantially transient" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear how the muting nucleic acid molecule can be maintained in a substantially transient manner. If the plasmids are only transiently present in the cells then they can not be maintained. The term maintained conveys a meaning of permanency. Claims 27 and 52 depend from claim 26.

Claims 1-27, 50 and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The terms "population of animal cells" and "population of cells" in claims 1 and 3 is a relative term which renders the claim indefinite. The term "population of cells" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear which cell types are targeted by the muting nucleic acid. The claim as written reads on both normal and pathogenic cell types.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-17 and 22-24 stand rejected under 35 U.S.C. 102(b) as being anticipated by Capecchi et al. The prior rejection of claims 1-17 and 22-24 is maintained for the reasons of record advanced Paper No. 5, on pages 11-13 of the Office action. Claim 50 as amended is encompassed by the standing rejection of claims 1-17 and 22-24 under 35 U.S.C. 102(b).

Applicant's arguments have been fully considered but they are not persuasive. Applicants argue that Capecchi does not teach the nucleic acid compositions of the claimed invention. Specifically, Applicants point out the claims 1-17 and 22-24 do not require a vector that carries a targeting gene which has been mutated to have a selectable marker. Applicants assert that the muting nucleic acid of the invention requires instead only a sequence that is homologous to an endogenous sequence. Applicants also argue that the method steps of the invention do not require any selection steps. See pages 9-11 of the amendment.

In response, the Examiner asserts that the claims are not distinguished from Capecchi. The product and method claims contain open claim language that does allow for the inclusion of selection markers, resistance genes, or selection steps. For example claim 1 merely requires a "nucleic acid sequence homologous to an endogenous sequence in the gene". Capecchi clearly teaches a nucleic acid sequence comprising a nucleotide sequence that is homologous to a nucleotide sequence of an endogenous gene. Homologous nucleotide sequences are the essence of Capecchi's targeting vectors. There is no difference between what Capecchi teaches and claim 1



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as it is written. Take claim 11 for example, the method as it is written only requires a muting nucleic acid and delivery of the same nucleic acid into a cell. Capecchi clearly teaches nucleic acid molecules that mute endogenous gene expression in a cell. It may be called "knocking out" or "muting" but for the purposes of this art rejection based on the claims as written "knocking out" or "muting" are the same. Accordingly, for the reasons of record and as discussed in the preceding paragraph, the rejection of claims 1-17 and 22-24 is maintained and also includes claim 50 as amended.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 8-10, 12, 17-21, and 25-27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al. The prior rejection of claims 1, 8-10, 12, 17-21, and 25-27 under 35 U.S.C. 103(a) is maintained for the reasons advanced in Paper No. 5 on pages 13-15 of the Office action. Claim 52 as amended is now included in the standing rejection of claims 1, 8-10, 12, 17-21, and 25-27 under 35 U.S.C. 103(a).

Applicant's arguments have been fully considered but they are not persuasive. Applicants argue that Capecchi differs from the claimed invention. Applicants argue that Capecchi does not teach or suggest a transient transfection, rather only a stable integration of a targeting vector. Applicants also argue that Capecchi teaches selection

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of the transfected cells which is not required by the claimed invention. Applicants further argue that Capecchi does not teach muting as defined by a reduction in gene expression. See pages 11-13 of the amendment.

In response, the Examiner maintains that the claims as written are not different and unobvious from the teachings of Capecchi. The product and method claims contain open claim language that does allow for the inclusion of selection markers, resistance genes, or selection steps. For example claim 1 merely requires a "nucleic acid sequence homologous to an endogenous sequence in the gene". Capecchi clearly teaches a nucleic acid sequence comprising a nucleotide sequence that is homologous to a nucleotide sequence of an endogenous gene. Homologous nucleotide sequences are the essence of Capecchi's targeting vectors. There is no difference between what Capecchi teaches and claim 1 as it is written. The requirement of "substantially transient" maintenance leaves open the possibility of a stable transfectant which meets the limitations of Capecchi. Accordingly, for the reasons of record and as discussed in the preceding paragraph the rejection of claims 1, 8-10, 12, 17-21, and 25-27 under 35 U.S.C. 103(a) is maintained and now includes claim 52 as amended.

### ***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Kay Pinckney whose telephone number is (703) 305-3553.

Peter Paras, Jr.

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*Scott D. Pinckney*  
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